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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/582,916	10/02/2000	Carl Anthony Blau	UOFW115624	4343

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1633	
MAIL DATE	**DELIVERY MODE**
10/30/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/582,916	BLAU ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-88* is/are pending in the application.

4a) Of the above claim(s) *43,54,67-69 and 77-88* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-42, 44-53, 55-66, and 70-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and response received on 8/21/07 have been entered. Claims 1-88 are pending in the instant application. This application contains claims 43, 54, 67-69, and 77-88 drawn to an invention nonelected **without** traverse in Paper No. 12. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01. Claims 1-42, 44-53, 55-66, and 70-76 are currently under examination. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in a previous office action.

37 CFR 1.121(c)

The amendment to the claims filed on 8/21/07 is objected to under 37 CFR 1.121(c). Claims 3, 23, and 45 contain the wrong claim identifier. Claims 3, 23, and 45 are listed as "withdrawn" in the 8/21/07 claim set. However, these claims were not withdrawn by the examiner and were under consideration and in "rejected" status prior to entry of this amendment. While the 8/21/07 amendment has been entered. Future amendments which do not comply with 37 CFR 1.121(c) will not be entered and the applicant will receive a letter of non-compliant amendment.

Claim Objections

The objection to claims 1-3, 5-23, 25-42, 44-45, 47-53, and 55 as be drawn to non-elected species is withdrawn over claims 1-2, 5-22, 25-42, 44, 47-53, and 55 in view of applicant's amendment of the claims limiting the mammalian cells to hematopoietic stem cells, and maintained over claims 3, 23, and 45 which list numerous non-elected species.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 23, and 45 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The independent claims from which claims 3, 23, and 45 depend have been amended to limit the cells to hematopoietic stem cells. However, claims 3, 23, and 45 recite a broader cell type of hematopoietic cells, or various unrelated cell types such that the limitations of claims 3, 23, and 45 conflict with that of the independent claims on which they depend. In addition, claims 3, 23, and 45 lack antecedent basis for "primary mammalian cells" as the independent claims upon which they depend no longer recite this phrase. Thus, the claims are indefinite as the metes and bounds of the claims cannot be determined.

Claim Rejections - 35 USC § 103

The rejection of claims 1-42, 59-66, and 70-76 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,741,899 (4/21/98), hereafter referred to as Capon et al., in view of Spencer et al. (1996) Current Biology, Vol. 6 (7), 839-847 and Blau et al. (1996) Blood, Vol. 88 (10 Suppl. 1 part 1-2), p542A, meeting abstract, hereafter referred to as Blau (1996), is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the grounds of rejection for reasons of record as discussed in detail below.

The applicant reiterates their previous arguments regarding the teachings of Capon et al. that the amount of dimerizing agent suggested by Capon et al. is ineffective to induce dimerization and that the skilled artisan following the teachings of Capon et al. would not know why the assay taught did not work and would have questioned the functionality of the chimeric receptors rather than the concentration of inducer used in the assay. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The rejection of record is based on the combined teachings of Capon et al. in view of Spencer et al. and Blau et al. Applicant's argument against Capon et al. is not persuasive because Blau et al. clearly teaches that in fact the chimeric receptors disclosed by Capon et al. were functional and capable of inducing dimerization and signaling leading to hematopoietic stem cell proliferation, and Spencer et al. teaches that varying the concentration of the inducer molecule FK1012 is a well established practice sufficient to identify a suitable

concentration of inducer to induce dimerization and signaling through a chimeric receptor in the cell line tested. Thus, the skilled artisan, familiar with Blau et al. would not question whether the chimeric receptors were functional. Instead, the skilled artisan, knowledgeable about the concentration affects of the inducer on signaling and proliferation as taught in Spencer et al., would simply have tested various concentrations of the inducer FKBP when practicing the methods of Capon et al.

The applicant further argues that Capon suggests JAK2 dimerization for transmitting a growth signal, but that others such as Mohi et al. (1998), submitted with the response, and Zhao et al. (2004), teach that JAK2 dimerization does not induce a growth signal unless the majority of the JAK2 molecule is deleted. In response, Capon et al. was not relied upon for teaching the use of JAK2 or any other member of the JAK kinase family as the signaling portion of the chimeric receptor. As set forth in the previous office action, Capon et al. was relied upon for teaching that the extracellular or intracellular inducer-responsive clustering domain of the chimeric protein is derived from immunophilin, e.g. FKBP, and that the cytoplasmic signal transduction domain is derived from homodimerizing receptors such as G-CSFR, EPO-R, GHR, PRLR, TPOR, and gp130 (Capon et al., columns 7, 9, 13, 15, 34-35, and 42-43). Whether or not JAK2 or other members of the JAK family are capable of transmitting growth dependent signals is irrelevant as Capon et al. was not relied upon for the use of any JAK family member as the cytoplasmic signaling domain. Further, Blau et al. provides specific evidence that dimerization of chimeric receptors comprising FKBP and EpoR leads to cell proliferation. It is also noted that while Mohi et al. was made available for consideration by the examiner, the post-filing art of Zhao et al. was not provided, is not of record, and thus was not considered.

The applicant then argues that Spencer uses mouse thymocytes in their experiments and that the chimeric receptors of Spencer induce apoptosis not cell proliferation. In response, the rejection of record acknowledged that the chimeric receptors in Spencer are different in that the cytoplasmic domains induce apoptosis not proliferation when dimerized. However, Spencer was relied upon for teaching specific concentrations of FK1012 which induce dimerization of chimeric proteins expressed by T cells comprising FKBP domains and Fas receptor leading to Fas receptor signaling and methods to determine the optimal concentration of FK1012 to induce the dimerization of chimeric proteins comprising FKBP and Fas receptor (Spencer et al., pages 841-843, Figures 1-3). While signaling through the Fas receptor induces cell death rather than proliferation, the essential teaching of Spencer is that FK1012 can be effectively used as a synthetic inducer of dimerization of chimeric receptor proteins comprising FKBP domains, that such dimerization leads to functional signaling through the receptor, and that the determination of concentrations of FK1012 capable of inducing dimerization was routine. Blau et al. was then cited to supplement the teachings of Capon et al. and Spencer et al. by teaching that FK1012 can also be used to induce dimerization of chimeric receptors comprising FKBP and EpoR leading to cell proliferation (Blau et al., abstract). Since Blau et al. does not specifically teach what concentration of FK1012 was used in their experiments that successfully induced dimerization and signaling leading to cell growth, the methods disclosed in Spencer simply provide the reasonable expectation that it would be routine to determine such an effective concentration of FK1012 as used in Blau et al.. It is further reiterated from previous office actions that in regards to the obviousness of optimizing concentrations, the MPEP, section 2144.05 which sets forth that, "[g]enerally, differences in concentration or temperature will not support the patentability of

subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. '[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.' *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)". See also *Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); and *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969), *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and *In re Geisler,* 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

The applicant further argues that the skilled artisan would not have been motivated to use FK1012 to treat cell transduced *in vivo* because FK1012 might bind to endogenous FKBP12 and the post-filing art of Neff and Blau et al. (2001) shows that FKBP12 knockout mice have sever congenital cardiomyopathy. In response, all three of the cited references teach the use of FK1012 as an effective inducer of dimerization of chimeric proteins comprising FKBP domains. Further, none of Capon et al., Spencer et al. or Blau et al. raise any concerns as to potential toxicity of FK1012 or teach away from its use *in vivo*. In addition, the instant claims encompass the use of FK1012 and are not limited to the embodiment of AP1903 referred to as being less toxic by the applicants. Finally, the post-filing evidence of Neff and Blau et al. was not provided to the examiner for consideration and is not of record. As such, the teachings of this reference could not be evaluated . However, it is noted that post-filing art cannot be relied upon to establish the state

of the art at the time of filing, and there is no evidence of record to suggest that the skilled artisan would have doubted that FK1012 would have been capable of dimerizing chimeric protein comprising FKBP domains *in vitro* or *in vivo*.

The applicant then argues that since the experiments in Blau et al. were performed *in vitro* and further used an established cell line and not a primary hematopoietic stem cell that the success reported by Blau et al. cannot be extrapolated to *in vivo* use. In response, it is first noted that Gene VI, Benjamin Lewin (1997) was not provided to the examiner, is not of record, and therefore has not been considered. Further, the claims as amended are not longer limited to "primary cells" but rather recite "hematopoietic stem cells" which encompasses any hematopoietic stem cell, whether primary or established as a cell line. Thus, the arguments regarding primary versus cultured cell lines and the references to Gene VI, Benjamin Lewin (1997), not of record, are not found persuasive. Further, claims 1-12, 21, 22-32, 41, and 59-62 are not limited to *in vivo* use, but are either composition claims, or methods that either specifically recite or encompass *in vitro/ex vivo* practice. Thus, applicant's arguments are not persuasive for these claims. For the remaining claims under consideration which do include the limitation of administering the inducer drug to transduced cell present *in vivo*, Capon et al. clearly teaches *in vivo* methods, and the successful demonstration of FK1012 induced cell proliferation reported by Blau et al. provides a reasonable expectation of success *in vivo* absent evidence to the contrary. Note that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See *In re O'Farrell*, 7 USPQ2d 1673 (CAFC 1988).

Thus, for the reasons discussed above, the rejection of record stands.

The rejection of claims 44-53, and 55-58 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,741,899 (4/21/98), hereafter referred to as Capon et al., in view of U.S. 5,994,313 (11/30/99), hereafter referred to as Crabtree et al., Spencer et al. (1996) Current Biology, Vol. 6 (7), 839-847, and Blau et al. (1996) Blood, Vol. 88 (10 Suppl. 1 part 1-2), p542A, meeting abstract, hereafter referred to as Blau (1996), is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the grounds of rejection for reasons of record as discussed in detail below.

Applicant's arguments regarding the teachings of Capon, Spencer, and Blau et al. were addressed in detail above and were not found persuasive. The applicant further argues that Crabtree et al. does not make up for the deficiencies in these references since Crabtree teaches chimeric receptors for inducing apoptosis not cell proliferation such that there is no motivation or teaching in the reference to modify the techniques to induce proliferation of stem cells. In response, it is first noted that claims 44-53 and 55 are product claims, not method claims, and are simply drawn to a genetically engineered mammalian hematopoietic stem cell. Claims 56-58, method claims, recite introducing these cells to a mammal and administering a dimerizing drug. As noted above, the claims as amended are no longer limited to "primary" cells. Further, Crabtree et al. was cited to supplement Capon regarding one specific aspect of the inducer-responsive clustering domain. The rejection of record notes that Capon et al. differs from the instant invention by not teaching that the inducer-responsive clustering domain (ICD) of the chimeric protein comprises at least one amino acid change compared to the most prevalent naturally-occurring amino acids sequence. However, Capon et al. does suggest that modifications

can be made to the ICD to create improved receptor-ligand binding (Capon et al., column 5, lines 12-15). Further, at the time of filing, various modifications to FKBP12s were known which increased their affinity or selectivity for their ligand. Crabtree et al. supplements Capon et al. by teaching similar chimeric proteins comprising an inducer-responsive clustering domain and a signaling domain where the inducer-responsive domain of FKBP12 contains specific amino acid changes as compared to the wild type sequences (Crabtree et al., column 23). Therefore, based on the motivation to make modifications to the ICD to create improved receptor-ligand binding provided by Capon et al., and the teachings of Crabtree et al. for specific single amino acid changes to FKBP12 to improve its binding affinity or specificity to ligand which can be used in chimeric signaling proteins, it would have been *prima facie* obvious to the skilled artisan at the time of filing to use one of the modified FKBP12 domains taught by Crabtree et al. in the chimeric proteins taught by Capon et al.. Further, based on the high degree of skill in the art of molecular biology at the time of filing, the skilled artisan would have had a reasonable expectation of success in making expression vectors encoding a chimeric protein comprising a modified FKBP12 and a proliferation signaling domain such as EpoR and in using those vectors to transfect/transduce hematopoietic stem cells according to Capon et al. Crabtree et al. was not relied upon for teaching hematopoietic stem cells modified to express specific chimeric receptors, Capon et al. and Blau et al. were relied upon for those teachings. Thus, there is no need to modify the techniques of Crabtree, as it is the methods of Capon that are to be modified by utilizing the modified FKBP12 domains of Crabtree et al.

Finally, applicant's discussion of the many inventive steps and extensive experimentation undertaken by applicants since the publication of the Blau et al. abstract, is not found persuasive

in overcoming the obviousness of the instant invention as claimed. The discussion of various receptors tested and the desirability of using a single drug binding domain rather than three FKBP12 domains is not persuasive as the claims are very broad, reciting the use of any signaling domain, and "at least one" drug-binding domain which reads on the use of three domains. Likewise the discussion of retroviral vectors is not persuasive as the claims broadly recite a "recombinant DNA construct".

Therefore, for the reasons discussed above, the rejection of record stands.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

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